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## Cytoreductive surgery after recurrent epithelial ovarian cancer and at other timepoints

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### Abstract

In this descriptive review we look at the role of surgery for advanced ovarian cancer at other timepoints apart from the initial cytoreduction for front-line therapy or interval cytoreductive surgery after neoadjuvant chemotherapy. The chief surgical problem to face after primary treatment is recurrent ovarian cancer. Of far more marginal concern are the second-look surgical procedures or the palliative efforts intended to resolve the patient's symptoms with no curative intent. The role of surgery in recurrent ovarian cancer remains poorly defined. Current data, albeit from non-randomized studies, nevertheless clearly support surgical cytoreduction in selected patients, a rarely curative expedient that invariably yields a marked survival advantage over chemotherapy alone. Despite these findings, some consider it too early to adopt secondary cytoreduction as the standard care for patients with recurrent ovarian cancer and a randomized study is needed. Two ongoing randomized trials (Arbeitsgemeinschaft Gynäkologische Onkologie-Desktop III and Gynecologic

Oncology Group 213) intend to verify the role of secondary cytoreduction for platinum-sensitive ovarian cancer compared with chemotherapy considered as standard care for these patients. We await the results of these two trials for a definitive answer to the matter.

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**Key words:** Ovarian cancer; Cytoreductive surgery; Recurrent ovarian cancer; Secondary cytoreduction; Surgery for Platinum sensitive ovarian cancer; Surgery for Platinum resistant ovarian cancer

**Core tip:** The chief surgical problem to face after primary treatment is recurrent ovarian cancer. The role of surgery in recurrent ovarian cancer remains poorly defined. Current data, albeit from non-randomized studies, nevertheless clearly support surgical cytoreduction in selected patients, a rarely curative expedient that invariably yields a marked survival advantage over chemotherapy alone. Despite these findings, some consider it too early to adopt secondary cytoreduction as the standard care for patients with recurrent ovarian cancer and a randomized study is needed.

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### INTRODUCTION

Recurrent disease is a challenging problem that sooner or later (within 18 mo after primary treatment) arises in about 80% of patients initially treated for advanced ovar-

ian cancer<sup>[1-3]</sup> and contributes substantially to the poor long-term outcome for this disease portending long-term survival in only 20%-30% of patients already at an advanced stage when diagnosed<sup>[4,5]</sup>.

Before considering the current options for treating patients with recurrent ovarian cancer we therefore deem it useful to analyze the possible reasons explaining why the disease recurs.

The natural history of ovarian epithelial malignancies shows that tumors originating from the epithelium lining the ovarian surface, and according to the most recent cytogenetic hypotheses also those arising from the epithelium covering the fallopian tubes and fimbria<sup>[6,7]</sup>, spread early to the peritoneum and locoregional lymph nodes<sup>[8]</sup>.

Peritoneal spread, frequently with ascites, follows a well-known anatomic course linked to peritoneal fluid dynamics leading neoplastic cells to colonize distant pelvic areas early thus making ovarian carcinoma the model for peritoneal spread from an intra-abdominal malignancy (Figure 1)<sup>[9,10]</sup>.

These pathophysiological events easily explain epidemiological data showing that when the disease is first diagnosed about 75% of women already have advanced ovarian cancer [International Federation of Gynecology and Obstetrics (FIGO) III-IV]<sup>[8]</sup> with major peritoneal and lymphatic spread obviously making the whole therapeutic strategy a complex task.

Although surgery and adjuvant chemotherapy remain the mainstay of treatment for advanced ovarian cancer the optimal therapeutic goal remains hard to reach<sup>[11]</sup>. Even though the specific single therapeutic role that each of the two principle procedures (surgery and adjuvant chemotherapy) covers in integrated treatment is difficult to investigate, we underline that the outcome benefits induced by platinum and its derivatives and paclitaxel (eventually given also by the intraperitoneal route) have presumably reached a plateau that appears arduous to improve until new effective anticancer drugs become available<sup>[12]</sup>.

Even though experience over years has recognized the prognostic importance of surgical cytoreduction (less residual disease = better outcome)<sup>[13]</sup>, a concept underlined in a meta-analysis conducted in recent years by Bristow *et al.*<sup>[14]</sup>, surgery remains the most highly variable and poorly standardized therapeutic factor, depending on the various surgical schools, the individual surgeon's cancer treatment policy and aims and finally on their technical skills.

Besides, some clinical oncologists, questioning whether surgery is really curative, despite convincing clinical evidence, hypothesize that whenever surgery achieves optimal disease control biological factors come into play and exert a determinant influence on the surgical outcome<sup>[15]</sup>. Going beyond these hypotheses if we want focus on the therapeutic potential of surgery in advanced ovarian cancer we have to analyze precisely what these surgical procedures aim to achieve and most important, how they are classified.

The surgical procedure for treating ovarian cancer is defined with the term "cytoreduction", a definition that seemingly implies residual disease after surgical debulking. Indeed, published studies invariably express their surgical results in terms of residual disease, using classifications that may overlap over time but nevertheless identify as "optimal cytoreduction" surgery leaving residual disease measuring 2 to 1 cm or less. In the latest Cochrane systematic review on this topic<sup>[11]</sup> the Gynecologic Oncology Group (GOG) currently defines optimal cytoreduction as residual tumor nodules "each" measuring 1 cm or less in maximal diameter underlining, however, the ideal surgical outcome as complete cytoreduction with no visible residual disease. The same review, analyzing experience gained in the most accredited world centers or most cited studies, underlines that surgery achieves this ideal outcome in only a mean 28% of the patients treated and most published surgical results describe residual disease ranging from less than 1 cm to more than 2 cm. Equally important, published surgical reports fail to quantify the overall number of residual lesions in each patient. Yet for two patients at the same disease stage both classified as optimally cytoreduced (residual disease measuring less than 1 cm) if one patient has 10 sites of residual disease and the other, for example, has more than 100 residua, outcomes can presumably differ. Similarly, in classification systems other than those used by the GOG (completeness of cytoreduction score, by Sugarbaker<sup>[16]</sup>) the lack of a variable quantifying the overall number of residual lesions creates substantial bias in analyzing the results because the group classified as optimally cytoreduced could comprise patients with differing amounts of residual disease. This drawback, already noted previously<sup>[17]</sup> but never investigated further, merits study to decide how to analyze the results in a more meaningful manner. Hence we reasonably presume that other clinical conditions (age, stage, performance status, platinum sensitivity, body surface area and therefore pharmacological dose) being equal, in two optimally cytoreduced patients in whom the number of residual lesions differs widely adjuvant chemotherapy will yield non-overlapping results.

All these observations prompt us to suggest that recurrent disease in advanced ovarian cancer should in many patients be more correctly interpreted as residual disease given that despite adjuvant chemotherapy surgery often leaves numerically rather than diametrically important residual lesions that ultimately manifest clinically as recurrence.

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## SECOND-LOOK SURGERY

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This term defines the surgical procedure used to confirm the response status in patients who are clinically disease-free after a front-line approach (primary cytoreduction and adjuvant chemotherapy). Second-look surgery is obviously not intended merely as a diagnostic procedure given that it envisages whenever possible resecting all clinically unrecognized disease eventually found.

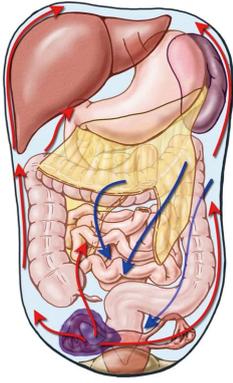


Figure 1 Peritoneal hydrodynamics.

The rationale underlying second-look surgery originally hinged on the concept that identifying residual disease foci early after front-line chemotherapy, removing them and consolidating the results with second-line chemotherapy improved survival. Positive histologic findings after second-look surgery directly reflect the initial disease stage and their percentage increases further in patients whose first operation leaves macroscopic residual disease<sup>[18]</sup>. Although second-look surgical procedures enjoyed wide use in the 1980s and 1990s their application gradually declined insofar as more than 50% of the patients identified at second-look surgery as complete responders within 12 to 24 mo thereafter went on to experience recurrent disease<sup>[19,20]</sup>. Randomized clinical trials have shown that although second-look procedures can accurately define patient responders they failed to increase survival<sup>[21]</sup>. An Italian study intended to investigate whether during a second-look procedure systematic aortic and pelvic lymphadenectomy had outcome advantages over a simple biopsy taken from clinically suspected lymph-node stations failed to show that either procedure improved outcome<sup>[22]</sup>.

In synthesis, current evidence therefore suggests that second-look surgery for ovarian cancer remains a useful therapeutic option when diagnostic investigations appear contrasting and can help ascertain the patient's clinical status and eventually treat the disease but should be reserved for individual patients and has no place as a general procedure. However, it may be a valid option for patients whom are detected during second-look surgery with platinum-resistant recurrent disease. If a complete macroscopic cytoreduction can be performed, patients will benefit as otherwise no real treatment options are available, in particular if hyperthermic intraperitoneal chemotherapy (HIPEC) can be added to the concept.

## SURGERY FOR PLATINUM-RESISTANT RECURRENT OVARIAN CANCER

Within 6 mo after undergoing treatment with the front-line approach (cytoreductive surgery plus primary adjuvant chemotherapy) 23% of patients with advanced

ovarian cancer experience recurrent disease<sup>[23,24]</sup>. Current consensus defines these patients as platinum-resistant. Platinum-resistance is a highly complex phenomenon that can develop during the natural history of the disease after initial platinum sensitivity. Studies conducted over recent years have emphasized the role played in chemoresistance by the so-called cancerous ovarian stem cells<sup>[25]</sup>. Previous surgery and chemotherapy in platinum-resistant patients seem to provide exceedingly disappointing results with a median survival of less than 10 mo<sup>[26-29]</sup>. This concern has now stimulated research efforts thus moving basic research into pharmacologic regimens towards promising advances using biological agents alone or combined with chemotherapy agents<sup>[30-32]</sup>.

From the viewpoint of the surgical approach, an extremely interesting new development seems to be the cumulative experience from two French groups who report in a large series of patients with recurrent ovarian cancer the surgical outcome after cytoreduction (peritonectomy procedures) and HIPEC and noted similar results in patients classified as platinum-sensitive and platinum-resistant<sup>[33]</sup>. These results seemingly underline the dual importance of endoperitoneal chemotherapy and concurrent hyperthermia. Endoperitoneal infusion undoubtedly has a pharmacokinetic advantage given that the "peritoneal plasma barrier" allows dose-intensity therapy and hyperthermia concurrently increases the chemotherapy agent's cytotoxic action and cell penetration perhaps overcoming problems related to platinum resistance<sup>[34,35]</sup>. If further confirmed these findings open the way to interesting future therapeutic advances, in particular because the mortality related to the procedure including HIPEC is low after absolving the learning curve although relevant morbidity is still frequent but most of it seems to be related to extended surgery. However, in HIPEC performed with oxaliplatin, postoperative bleeding after 7-10 d following surgery can be a serious complication in up to one third of all patients requiring a reoperation<sup>[36]</sup>.

## SURGERY FOR PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER

The 4<sup>th</sup> ovarian cancer consensus conference held in 2010 stated that surgery might be appropriate in selected patients with platinum-sensitive recurrent ovarian cancer and might be beneficial if it achieved complete resection<sup>[24]</sup>. The therapeutic value of repeating the initial surgical treatment (cytoreduction) in patients with advanced ovarian cancer who will experience tumor recurrence remains debatable. Since Berek *et al.*<sup>[37]</sup> in 1983 first introduced the term "secondary cytoreduction" many papers published over the ensuing years have addressed this topic<sup>[38-44]</sup> and in recent years some investigators have even introduced the concept tertiary cytoreduction<sup>[45,46]</sup>. Secondary cytoreduction after an extended treatment-free interval (from 6 to 12 mo or more) can increase survival (though rarely leads to a definitive cure) because the cytoreductive effect sums up with an improved response

to subsequent chemotherapy<sup>[47]</sup>. But beyond single series, the potential usefulness of secondary cytoreduction after primary treatment remains controversial: most studies are retrospective, come from single centers, often enrol fewer than 100 cases, cover a long time-span and most important, are non randomized<sup>[48]</sup>. To address these doubts Bristow *et al*<sup>[47]</sup> conducted a meta-analysis investigating the prognostic importance of several variables on overall survival in 40 patient cohorts (2019 cases) undergoing secondary cytoreduction for platinum-sensitive recurrent ovarian cancer. They used simple and multiple regression analyses, with weighted correlation calculations and after controlling for all other factors, each 10% increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3.0 mo increase in median cohort survival time. The investigators concluded that among patients undergoing surgery for recurrent ovarian cancer, the proportion of patients achieving complete cytoreductive surgery is independently associated with overall post-recurrence survival time. The same study showed that other more strictly surgery-related variables such as operative time, blood loss, surgical morbidity and mortality were comparable with the data generally reported for primary cytoreduction, coming within an acceptable percentage of risk.

Yet given that outcome improves only in patients in whom surgery achieves complete cytoreduction, an inherent limitation in their meta-analysis, as Bristow *et al*<sup>[47]</sup> themselves admit, is the inability to define a correct profile for patients in whom they can achieve this aim and for whom we should reserve the surgical option. Two studies in recent years seem to answer this question by developing a risk model for predicting complete secondary cytoreductive surgery in patients with platinum-sensitive recurrent ovarian cancer. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Desktop I study<sup>[40]</sup> evaluated three predictive factors for complete resection: good performance status (ECOG 0), complete resection at first surgery, absence of ascites and in the subsequent AGO-Desktop II study<sup>[49]</sup> this score was validated prospectively: if all three factors are present complete resection is feasible in 76% of the patients. A second risk model was developed in 1075 patients by an International Collaborative Cohort study<sup>[50,51]</sup> that partly integrated the previous model by evaluating the progression-free interval, the Ca 125 level and the FIGO stage. From these overall data they extrapolated two categories, patients at low risk (score  $\leq 4.7$ ) in whom complete cytoreduction is possible in 53% to 83% of the cases and those at high risk (score  $> 4.7$ ) in whom surgery can achieve complete cytoreduction in from 20% to 42% (Table 1).

Despite these findings, some consider it too early to adopt secondary cytoreduction as the standard care for patients with recurrent ovarian cancer and a randomized study is needed<sup>[52]</sup>. Two ongoing randomized trials (AGO-Desktop III and GOG 213) intend to verify the role of secondary cytoreduction for platinum-sensitive ovarian cancer compared with chemotherapy considered

**Table 1 Risk model for secondary cytoreductive surgery in patients with recurrent ovarian cancer based on the international collaborative cohort**

Impact factors	Scoring				
	0	0.8	1.5	1.8	2.4
FIGO stage	I / II		III / IV		
Residual disease at 1 <sup>st</sup> surgery	0		> 0		
Progression-free interval (mo)	> 16			< 16	
ECOG performance status	0-1			2-3	
Ca 125 at recurrence (U/mL)	< 105			> 105	
Ascites at recurrence	Absent				Present

Low risk  $\leq 4.7$ , complete resection feasible from 53% to 83%; high risk  $\geq 4.7$ , complete resection feasible from 20% to 42%. FIGO: International Federation of Gynecology and Obstetrics; ECOG: Eastern Cooperative Oncology Group.

as standard care for these patients. We await the results of these two trials for a definitive answer to the matter.

For patients following complete cytoreduction, HIPEC may be beneficial as suggested by a recent paper from France<sup>[33]</sup>. In the largest HIPEC series for persistent and recurrent ovarian cancer, including 246 patients, the median survival following surgical cytoreduction and HIPEC was 48.9 mo. Mortality was in this group very low with 0.37% and morbidity of 11.6%.

For platinum-sensitive recurrent disease, two other European prospective randomized trials are investigating at present the role of HIPEC. One trial is the French trial CHIPOR study: all patients get first neoadjuvant systemic chemotherapy and surgical cytoreduction. Following surgery, patients are randomized to HIPEC (cisplatinum 75 mg/m<sup>2</sup>) *vs* no HIPEC. The other trial is the Italian trial HORSE with a similar design, however, without neoadjuvant systemic chemotherapy and the same cisplatinum dose as in the French trial<sup>[53]</sup>.

In conclusion, although surgical techniques and chemotherapy regimens used to treat ovarian cancer have advanced remarkably over the past several decades, despite the best efforts the 5-year survival rate has improved by only 8% since 1975<sup>[54]</sup>.

The proportion of patients with advanced ovarian cancer who relapse has remained high and fairly constant and because cure is rarely possible, key objectives are to maintain and improve quality of life and prolong survival. Patients commonly undergo multiple chemotherapy courses<sup>[55]</sup> intended to overcome the platinum resistance that follows initial platinum sensitivity, control symptoms and allow disease chronification.

The role of surgery in recurrent ovarian cancer remains poorly defined. Current data, albeit from non-randomized studies, nevertheless clearly support surgical cytoreduction in selected patients, a rarely curative expedient that invariably yields a marked survival advantage over chemotherapy alone<sup>[50,56]</sup>.

Although we realize that scientific research requires level 1 evidence to conclude that one therapeutic option is better than another, randomizing a patient with recurrent ovarian cancer who is technically operable (the Desktop III protocol requires as an inclusion criterion scores known to predict complete cytoreduction) could raise ethical doubts and probably does nothing to help patient accrual.

And finally, the latest advances from studies investigating the pathogenesis of ovarian cancer clearly show that a “blanket approach” to ovarian cancer treatment is insufficient<sup>[7]</sup>. The key future turning point for guaranteeing effective treatment depends on developing target therapies designed to exploit the molecular and genetic characteristics of individual tumor subtypes. These observations raise further doubts on the appropriateness of randomized trials enrolling patients whose tumors differ widely in biological features.

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